Environmental Standards for Ionizing Radiation: Theoretical Basis for Dose-Response Curves

by Arthur C. Upton*

The types of injury attributable to ionizing radiation are subdivided, for purposes of risk assessment and radiological protection, into two broad categories: stochastic effects and nonstochastic effects. Stochastic effects are viewed as probablistic phenomena, varying in frequency but not severity as a function of the dose, without any threshold; nonstochastic effects are viewed as deterministic phenomena, varying in both frequency and severity as a function of the dose, with clinical thresholds. Included among stochastic effects are heritable effects (mutations and chromosome aberrations) and carcinogenic effects. Both types of effects are envisioned as unicellular phenomena which can result from nonlethal injury of individual cells, without the necessity of damage to other cells. For the induction of mutations and chromosome aberrations in the low-to-intermediate dose range, the dose-response curve with high-linear energy transfer (LET) radiation generally conforms to a linear nonthreshold relationship and varies relatively little with the dose rate. In contrast, the curve with low-LET radiation generally conforms to a linear-quadratic relationship, rising less steeply than the curve with high-LET radiation and increasing in slope with increasing dose and dose rate. The dose-response curve for carcinogenic effects varies widely from one type of neoplasm to another in the intermediate-to-high dose range, in part because of differences in the way large doses of radiation can affect the promotion and progression of different neoplasms. Information about dose-response relations for low-level irradiation is fragmentary but consistent, in general, with the hypothesis that the neoplastic transformation may result from mutation, chromosome aberration or genetic recombination in a single susceptible cell.

Introduction

The relationship between the dose of an environmental agent and the biological response it may elicit can vary, depending on the response, the conditions of exposure and variables affecting susceptibility (1–5). The last include the effectiveness of repair processes and other systems capable of modifying the response. In the case of chemicals, including radionuclides, such variables include factors influencing the uptake, distribution, concentration, and metabolic fate of the substances in question (1, 2, 4). With some chemicals, moreover, as opposed to radionuclides or ionizing radiation, toxicity also depends on the balance between enzymatic activation and inactivation (1–3, 6).

Consideration of dose-response relationships must take into account each of the above sources of variation, which involves many uncertainties in our present state of knowledge (1–7). Hence, efforts to define the mathematical relationship between dose and effect under conditions of low-level exposure in human populations must be based on assumptions and extrapolations of unproven validity. The scientific basis on which dose-effect relationships of ionizing radiation have been analyzed, for purposes of radiological protection, are surveyed briefly in this report.

Diversity of Effects To Be Considered

To assess the health impact of a given effect of ionizing radiation, or another environmental agent, the following questions must be addressed:

*Department of Environmental Medicine, New York University School of Medicine, 550 First Avenue, New York, NY 10016.

(1) Is the effect reversible or irreversible? (2) Is it stationary or progressive? (3) What is the relation between its frequency (and severity) and the dose—is there a threshold? (4) How are its frequency and severity influenced by the distribution of the dose in space and time? (5) How is susceptibility to the effect influenced by age at exposure, sex, genetic constitution, and other physiological factors? (6) How is the frequency or severity of the effect influenced by other environmental agents—are synergistic interactions with other agents known or suspected to occur? Complete answers to these questions are seldom possible in our present state of knowledge. Nevertheless, for purposes of radiological protection, radiation effects are generally divided into stochastic effects and nonstochastic effects (8).

Stochastic effects are viewed as probablistic in nature, varying in frequency, but not severity, as a function of the dose, without any threshold. Nonstochastic effects, in contrast, are viewed as deterministic phenomena, varying in both frequency and severity as a function of the dose. Stochastic effects include genetic (heritable) and carcinogenic effects, both of which are envisioned to result from nonlethal damage to individual cells. Nonstochastic effects, on the other hand, are envisioned to reflect tissue damage resulting from the collective injury or killing of many cells in the affected organs. Familiar examples include cataract of the lens, impairment of fertility, atrophy of blood-forming organs and nephrosclerosis. Teratogenic effects on the developing embryo are viewed largely as nonstochastic in nature, although the possibility that some such effects are stochastic cannot be excluded (4, 5, 8).

Studies of the mechanisms of the various radiation effects in experimental animals, analyzed in the light of relevant epidemiological observations in human populations, provide a scientific basis for assessing dose-response relationships for purposes of radiological protection, as discussed below.

Stochastic Effects

Genetic Effects

Genetic or heritable effects include point mutations and changes in chromosome number and structure. Each of these types of effects results from physicochemical changes caused by the passage of one or more ionizing particles through, or close to, the affected gene or chromosome (5, 9–11).

Damage to DNA

The changes in genes and chromosomes are associated with lesions in DNA which include single-strand and double-strand breaks, crosslinks, and various alterations in sugar and base moieties (5, 10). The majority of such lesions in DNA appear to repairable through the action of enzyme systems normally present in diploid mammalian cells (11, 12). Hence, the biological significance of a given lesion may depend as much on the way in which it is repaired, or misrepaired, as on the nature of the initial lesion itself. Although chromosome aberrations are generally assumed to result from double-strand breaks in DNA (5, 13), the molecular basis for a given heritable effect of radiation cannot yet be specified in detail.

Mutations

From a wealth of experimental studies, the frequency of mutations is inferred to increase as a linear, nonthreshold function of the dose of radiation, implying that mutation can result from traversal of the genetic material by a single ionizing particle. In mouse spermatogonia and oocytes, however, the mutation frequency varies with the dose rate of low linear energy transfer (LET) radiation (Figs. 1 and 2) (14), indicating that the probability of mutational damage resulting from traversal by a single low-LET radiation track is disproportionally smaller than that resulting from traversal by two or more such tracks in swift succession. This relationship, and the steeper dose-effect curve characteristic of high-LET radiation, imply that the damage resulting from traversal by a single low-LET radiation track, as opposed to a high-LET radiation track, is usually repairable (4, 5).

Another noteworthy feature of the curves is the enhanced yield of mutations per unit dose that may result from appropriately fractionated exposures to low-LET radiation (Fig. 1) (14). Although this enhancement remains to be explained conclusively, it indicates that susceptibility to genetic damage may, under certain conditions, be increased by a previous exposure, possibly through effects on cell population kinetics and/or repair processes.

Also noteworthy is the tendency for the mutation frequency to pass through a maximum at intermediate-to-high doses and to decline with further increase in the dose, when the radiation is accumulated at high dose rates (Figs. 1 and 2) (14). The saturation of the curves at high dose rates is attributed to interference with expression of the induced mutations because of excessive cellular damage (5).

An additional feature to be noted is the reduced yield of mutations in offspring conceived by females more than 7 weeks after irradiation (Fig. 2) (*14*). This reduction denotes marked differences in susceptibility among various oocyte maturation stages, presumably because of variations in repair capability, yet to be defined. Such differences seriously complicate extrapolation to other animals, including humans, in view of known species differences in the kinetics of oocyte maturation (*5*).

Chromosome Aberrations

As with the dose-response curve for mutations, the dose-response curve for chromosome aberrations conforms to a linear nonthreshold function with high-LET radiation, and to a linear-quadratic function with low-LET radiation (Fig. 3) (*15*). These relationships can be represented by the expression:

$$Y = C \times aD \times bD^2 \qquad (1)$$

where Y is the frequency of aberrations after dose D, C is the frequency in nonirradiated cells, and a and b are coefficients of linear and quadratic dose terms, respectively. With high-LET radiation, the ratio a/b is such that the linear term (aD) predominates at all doses. With low-LET radiation, the ratio of a/b for mammalian cells is generally of the order of 100–150—namely, $10^{-4}/10^{-6}$—so that the linear term (aD) predominates at doses below 100–150 rads and the quadratic term (bD^2) at higher doses (*9, 15*).

From these relationships it can be inferred that the probability of producing two chromosome breaks close enough together in space and time to give rise to an interchange aberration is disproportionally smaller for traversal by a single low-LET radiation track than for two such traversals in swift succession, and that a single low-LET radiation traversal characteristically deposits enough localized energy for such an effect only at the ends of its delta tracks.

Carcinogenic Effects

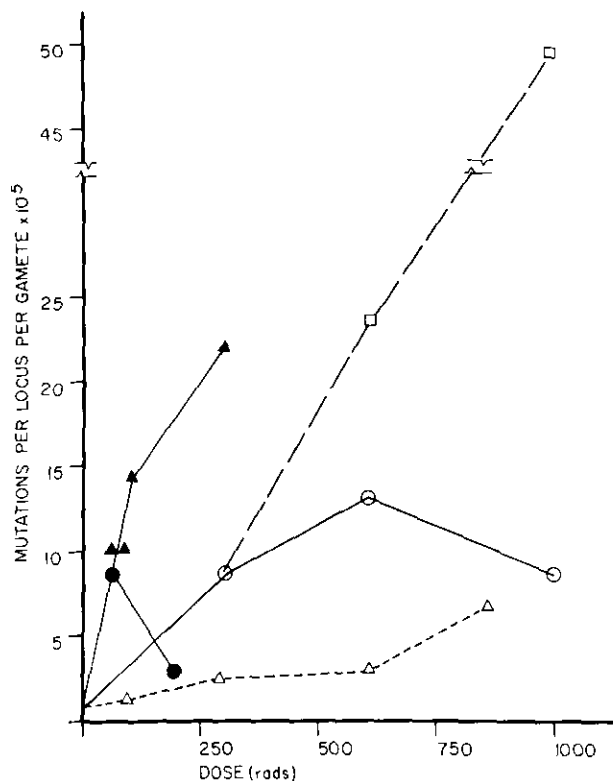In experimental animals exposed at intermedi-

FIGURE 1. Frequency of specific-locus mutations in mouse spermatogonia as a function of the dose and dose rate of irradiation: (●, ▲) data for neutrons; (○, □, △) data for X-rays and γ-rays; (○) data for acute exposures; (□) data for fractionated exposures; (△, ▲) data for chronic, daily exposures (*14*).
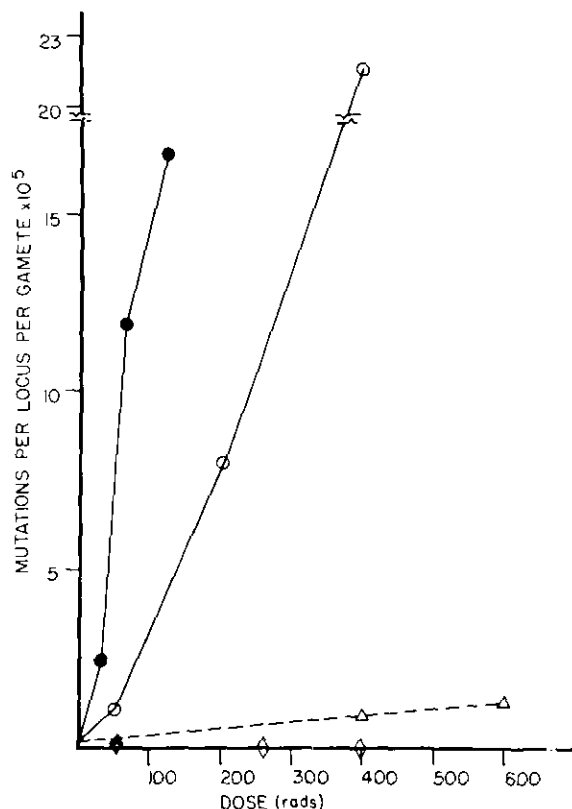

FIGURE 2. Frequency of specific-locus mutations in mouse oocytes as a function of the dose and dose rate of irradiation. Symbols are the same as in Figure 1; (◇) data for matings more than 7 weeks after irradiation (*14*).
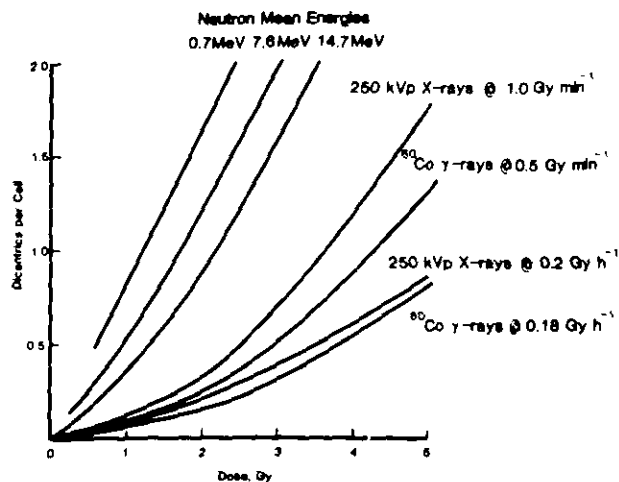
FIGURE 3. Frequency of dicentric chromosome aberrations in human lymphocytes irradiated *in vitro*, as a function of the dose and dose rate of neutrons, X-rays, and γ-rays (15).

FIGURE 4. Rate of hamster embryo cell transformation *invitro* in relation to dose of argon ions, neutrons, or X-rays (23).

ate to high doses, the dose-response relation for carcinogenesis varies, depending on the type of neoplasm, the conditions of irradiation, and the susceptibility of the exposed population (4, 5). To some extent, the variations may be attributed to the diversity of effects through which large doses of radiation can conceivably promote tumor formation. These include changes in cell population kinetics, disturbances in endocrine balance, depression of immunity, and other alterations affecting tissue homeostasis (5, 16). In view of the multistage nature of carcinogenesis and the many factors that can influence the progression of the cancer process, one would not expect the yield of neoplasms per unit dose to be the same for all tissues, organs, individuals, doses, and conditions of irradiation (5, 16-18).

In the low-dose region, the carcinogenic action of radiation is attributable to a narrower range of effects, since injury of far fewer cells can be presumed to be involved. In fact, if the neoplasm induced by a small dose of radiation is assumed to be monoclonal in origin and to arise from the neoplastic transformation of a single cell by damage to its genes or chromosomes, then the dose-response relationships for such oncogenic effects should in principle be consistent with those characteristic for the induction of mutations and chromosome aberrations described above.

The dose-incidence curves for most radiation-induced neoplasms in experimental animals are, in fact, consistent with the dose-response curves for induction of mutations and chromosome aberrations, in that: (1) the curves with high-LET radiation are steeper, more nearly linear, and less
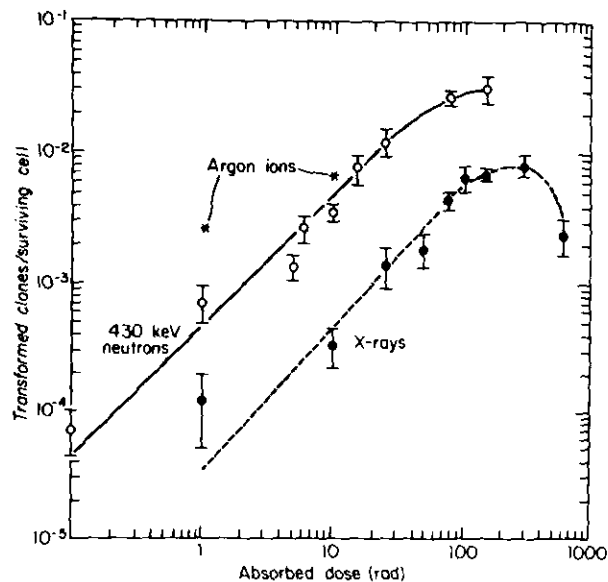
dependent on the dose rate than are the curves with low-LET radiation; (2) the curves with low-LET radiation tend to increase in slope with increasing dose and dose rate; and (3) the curves with both types of radiation tend to pass through a maximum at intermediate to high doses and to decrease with further increase in the dose (5, 16). These relationships can be represented by the expression:

$$y = (c + aD + bD^2)e - (pD + qD^2) \qquad (2)$$

where y is the cumulative incidence of neoplasms, D s the dose, C is the spontaneous incidence, a and b are coefficients of linear and quadratic dose terms for cancer induction, and p and q are coefficients of linear and quadratic dose terms for cell killing (16–19).

Interpretation of the similarities between the dose-response relationships for induction of neoplasms and those for induction of mutations and chromosome aberrations is complicated by the fact that the data derived from experimental animals have been obtained largely at intermediate to high doses, where the promoting effects of cell killing or other forms of injury may contribute significantly to carcinogenesis. In view of the multistage nature of the cancer process and our uncertainty as to the mechanism(s) of carcinogenesis at low doses, the actual shape(s) of the dose-response curve(s) for low-level radiation carcinogenesis remain(s) to be defined.
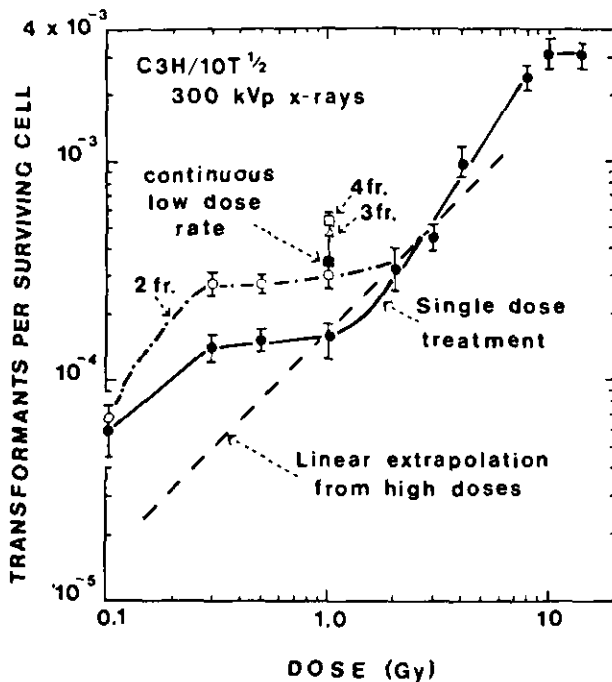
FIGURE 5. Frequency of transformation in C3H — 10T1/2 mouse embryo fibroblasts irradiated *in vitro,* in relation to dose of X-rays and conditions of irradiation *(26).*
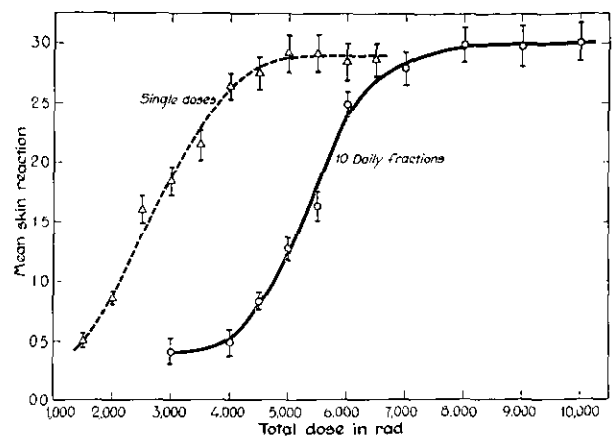

FIGURE 6. Dose-response curves for skin reactions in the mouse foot for single doses and for 10 daily fractions. For single doses, the mean skin reaction was obtained by averaging the daily skin reaction scores for days 8 to 29 post irradiation. For the fractionated treatment, the scores were averaged over a period of 13 to 34 days from the start *of treatment. Scores are as follows: 0.5, no definite effect;* 1.0, slight reddening; 1.5, small areas of skin breakdown, with scaling, crusting, puffiness, and/or severe redness; 2.0, moderate areas of skin breakdown, with small areas of moist exudate; 2.5, large areas of skin breakdown, with *considerable moist exudate; 3.0, most of skin affected by* breakdown and moist exudate; 3.5, complete necrosis of limb *(30, 31).*

Also complicating extrapolation into the low dose domain is evidence, for certain types of neoplasms, that the incidence per unit dose of high-LET radiation may increase with decreasing dose and dose rate, giving a dose-effect curve that is convex upward *(20–22).* While such a "supralinear" dose-response relationship might be attributable to heterogeneity in susceptibility among individuals in the population at risk, such an explanation remains speculative at present.

Efforts to analyze the dose-response relation by investigating the kinetics of neoplastic transformation of cells *in vitro,* uncomplicated by tissue variables, have revealed curves that tend to have some features in common with those obtained *in vivo;* namely, (1) the yield of transformants per unit dose is higher with high-LET radiation than with low-LET radiation; (2) the yield of transformants per unit dose of low-LET radiation generally increases with increasing dose and dose rate; and (3) the yield of transformants with both types of radiation passes through a maximum at intermediate to high doses and decreases with further increase in the dose (Fig. 4) *(23).* While it is tempting to relate these resemblances between transformation *in vitro* and carcinogenesis *in vivo* to a common underlying mechanism, such as the induction of mutations or chromosomal aberra-

tions, this interpretation is complicated by evidence that the frequency of transformation *in vitro* can be affected by cell plating density, time between irradiation and subcultivation, concentration of serum in the culture medium, and other variables, the effects of which remain to be explained *(24, 25).* It is noteworthy, for example, that the frequency of transformants per unit dose may be higher in embryo fibroblasts exposed *in vitro* to 0.5–1.5 Gy when the dose is delivered in two equal fractions separated by a 5-hr interval or is protracted over a 6-hr period, than when the dose is delivered in a single brief exposure (Fig. 5) *(26),* for reasons yet to be determined. Analysis of the kinetics of the production and repair of injury *leading to transformation in vitro, as compared with the induction of mutations, chromosome aberrations and cell killing, may help to elucidate the relationships among these effects in the not-too-distant future (27).*

Another difficulty complicating characterization of the dose-response relationship is uncertainty about the distribution of radiation-induced neoplasms as a function of the dose of radiation and the time after exposure. When a dose is received in a single brief exposure, the time elapsing until the appearance of the induced neoplasms varies, depending on the type of neoplasm

in question, age at irradiation, and other factors (4, 5). When a dose is accumulated over a prolonged period, displacement in the temporal distribution of neoplasms may reflect the influence of these and other variables, the iteracting effects of which are not yet well known (17, 18, 28). Thus, the duration of the "latent period" preceding the appearance of radiation-induced neoplasms, the duration of the "plateau period" when such neoplasms can be expected to appear in an exposed population, and the magnitude of the increase in incidence at various times during the "plateau period" cannot be confidently predicted in any given situation from the limited information now available. Heuristic models have involved various simplifying assumptions about the duration of the "latent" and "plateau" periods. One such model—the so-called "relative risk" model—assumes that the carcinogenic effects of a given dose are expressed during the "plateau" period as a constant increase in the relative risk of cancer in those of differing ages, or as a constant multiple of

the spontaneous age-specific incidence (4). Another model—the so-called "absolute risk" model—assumes, on the contrary, that the number of radiation-induced neoplasms is the same for a given dose, irrespective of age-related changes in the natural incidence within the population at risk (4). Each model fits the data for certain types of neoplasms better than the other model, but both models are little more than oversimplifications at best.

Nonstochastic Effects

In contrast to stochastic effects, nonstochastic effects are expected to remain subclinical except at doses above presumed thresholds. Since, however, the production of nonstochastic effects involves various stochastic effects, including the killing of cells (29), the dose-response relationship for any given nonstochastic effect will depend on the stage at which it is scored. The relation between the severity of acute skin dam-
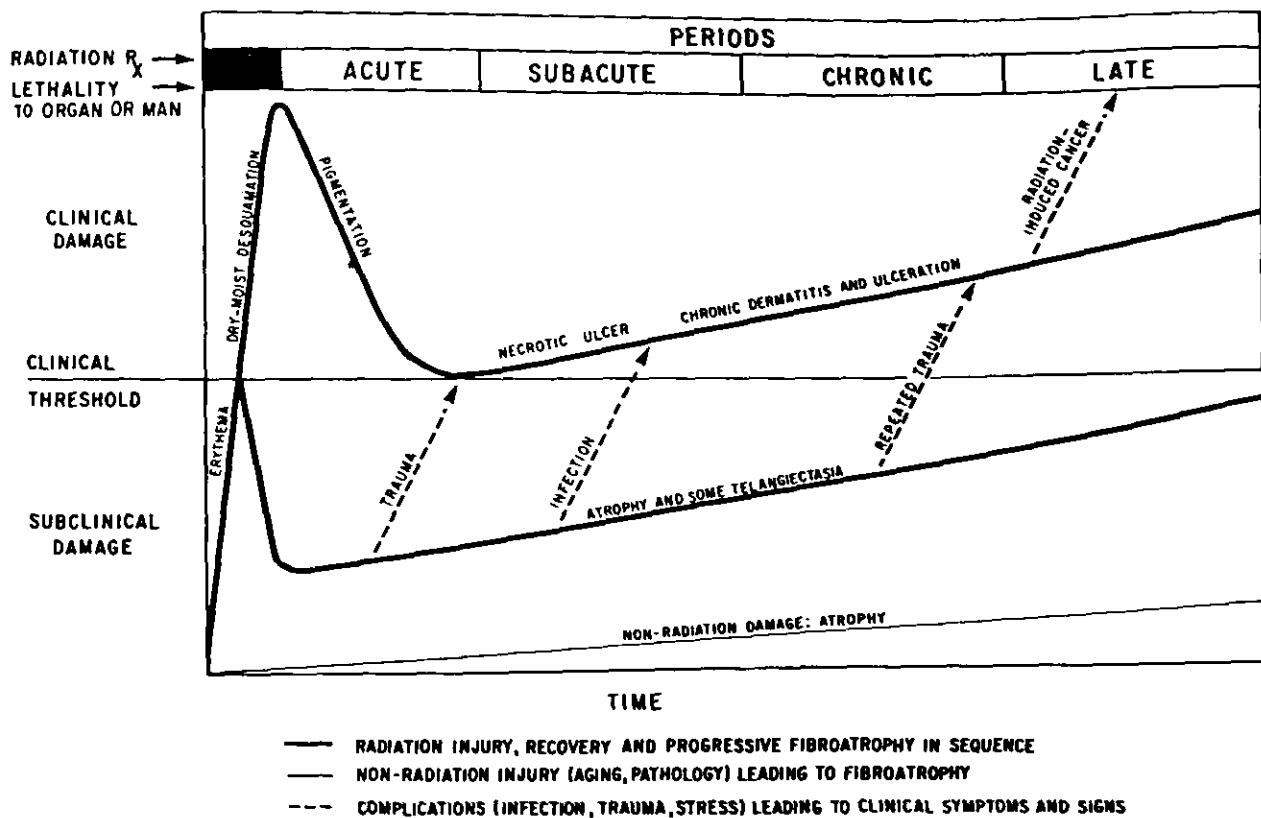
FIGURE 7. Diagrammatic representation of the course of two possible skin reactions after relatively heavy irradiation, viewed in relation to time and the natural aging process. The upper line illustrates the development of clinical complications, the middle line illustrates a reaction that does not reach the clinically defined threshold. Trauma or infection may unmask latent injury, however, since irradiated tissue may have reduced healing ability (32).

Table 1. Estimated doses required to cause various types of tissue damage within five years after irradiation.[a]

Organ	Injury at 5 years	1-5% TD$_{5/5}$	25-50% TD$_{50/5}$	Fraction of organ irradiated
Skin	Ulcer, severe fibrosis	5,500	7,500	100 cm^3
Oral mucosa	Ulcer, severe fibrosis	6,000	7,500	50 cm^3
Esophagus	Ulcer, stricture	6,000	7,500	75 cm^3
Stomach	Ulcer, perforation	4,500	5,000	100 cm^3
Intestine	Ulcer, stricture	4,500	6,500	100 cm^3
Colon	Ulcer, stricture	4,500	6,500	100 cm^3
Rectum	Ulcer, stricture	5,500	8,000	100 cm^3
Salivary glands	Xerostomia	5,000	7,000	50 cm^3
Liver	Liver failure, ascites	3,500	4,500	Whole
Kidney	Nephrosclerosis	2,300	2,800	Whole
Bladder	Ulcer, contracture	6,000	8,000	Whole
Ureters	Stricture, obstruction	7,500	10,000	5-10 cm
Testes	Permanent sterilization	200-600	2,000	Whole
Ovary	Permanent sterilization	200-300	625-1,200	Whole
Uterus	Necrosis, perforation	<10,000	<20,000	Whole
Vagina	Ulcer, fistula	9,000	<10,000	5 cm
Breast				
Child	No development	1,000	1,500	5 cm^3
Adult	Atrophy + necrosis	<5,000	<10,000	Whole lobe
Lung	Pneumonitis, fibrosis	4,000	6,000	
Capillaries	Telangiectasia, sclerosis	5,000-6,000	7,000-10,000	
Heart	Pericarditis, pancarditis	4,000	<10,000	Whole
Bone				
Child	Arrested growth	2,000	3,000	10 cm^3
Adult	Necrosis, fracture	6,000	15,000	10 cm^3
Cartilage				
Child	Arrested growth	1,000	3,000	Whole
Adult	Necrosis	6,000	10,000	Whole
CNS (brain)	Necrosis	5,000	<6,000	Whole
Spinal cord	Necrosis, transection	5,000	<6,000	5 cm^3
Eye	Panophthalmitis, hemorrage	5,500	10,000	Whole
Cornea (L.B.)	Keratis	5,000	<6,000	Whole
Lens	Cataract	500	1,200	Whole
Ear (inner)	Deafness	<6,000	—	Whole
Vestibular	Meniere's	6,000	10,000	Whole
Thyroid	Hypothyroidism	4,500	15,000	Whole
Adrenal	Hypoadrenalism	<6,000	—	Whole
Pituitary	Hypopituitarism	4,500	20,000-30,000	Whole
Muscle				
Child	No development	2,000-3,000	4,000-5,000	Whole
Adult	Atrophy	<10,000	—	Whole
Bone marrow	Hypoplastic	200	550	Whole
		2,000	4,000-5,000	Localized
Lymph nodes	Atrophy	3,500-4,500	<7,000	Localized
Lymphatics	Sclerosis	5,000	<8,000	Localized

[a]Modified from Rubin and Casarett (*33*). Tabulated levels are estimates of dose required to cause an incidence of 5% (TD$_{5/5}$) or 50% (TD$_{50/5}$), respectively, of effects, with the following radiation conditions: super-voltage therapy (1–6 MeV); 1000 rad/week in five daily fractions with a 2-day rest; and treatment completed in 2-8 weeks, depending on the total dose.

age, the radiation dose, and the duration of exposure is shown schematically in Figure 6 (*30, 31*).

In contrast to stochastic effects, nonstochastic effects are expected to remain subclinical except at doses above presumed thresholds. Since, however, the production of nonstochastic effects involves various stochastic effects, including the killing of cells (*29*), the dose-response relationship for any given nonstochastic effect will de-pend on the stage at which it is scored. The relation between the severity of acute skin damage, the radiation dose, and the duration of exposure is shown schematically in Figure 6 (*30, 31*). In general, except for teratogenic effects, the dose-response relation for nonstochastic effects of clinical severity is highly sigmoid, with thresholds in the range of 1-20 Gy. For teratogenic effects on the developing embryo, effects well below 1 Gy

have been observed, with evidence for a high relative biological effectiveness of high-LET radiations (5).

In considering dose-response relationships for nonstochastic effects, it must be remembered that some such effects develop slowly (Fig. 7) (32), with the result that assessment of their dose-response relationships must take into account the long time required for their evolution.

In general, the doses required to cause nonstochastic effects are large enough (Table 1) (33) so that it is feasible to prevent their occurrence in radiation workers by limiting the cumulative occupational lifetime exposure to subthreshold levels (8).

Teratogenic effects on the developing embryo are generally attributed to the depletion of progenitor cells in embryonic anlage at critical stages in organogenesis. To the extent that killing of appreciable numbers of cells in such anlage is required to induce malformation, and that the stages of maximum susceptibility to cell depletion are sharply delimited in time, thresholds for most such effects are presumed to exist (4, 5).

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